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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,335	01/15/2004	Seth J. Orlow	71369.368 and PFI-016CIPD	6410
23483	7590	07/06/2006	EXAMINER	
WILMER CUTLER PICKERING HALE AND DORR LLP 60 STATE STREET BOSTON, MA 02109			ANDERSON, JAMES D	
			ART UNIT	PAPER NUMBER
			1614	

DATE MAILED: 07/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/758,335

Applicant(s)

ORLOW ET AL.

Examiner

James D. Anderson

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-77 is/are pending in the application.
- 4a) Of the above claim(s) 1-43 and 70-77 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-69 is/are rejected.
- 7) ☒ Claim(s) 47 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12 sheets.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Informalities

Claims 1-77 are currently pending and are the subject of this Office Action. Claims 1-43 and 70-77 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 44-69 are pending and are being examined on the merits.

Information Disclosure Statement

Several references were not considered in the information disclosure statement filed February 20, 2004 because they fail to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Several references are missing the year of publication whereas others only list page numbers but no year or volume number. Some books listed on the IDS have not been considered because the citation does not refer to the pertinent pages. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Election/Restrictions

Applicant's election without traverse of Group III, claims 44-56 and 57-69, in the reply filed on April 25, 2006 is acknowledged.

Claim Objections

Claim 47 is objected to because of the following informalities: in line 21, the claim recites the limitation "R6". This appears to be a typo because other R groups are designated ----R_x--- as found in the compound of Formula (I) and claim 60, line 5.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-47, 49, 57-60 and 62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of decreasing melanin production and reducing skin pigmentation with compounds that "effect[s] an alteration in late endosomal/lysosomal trafficking" (page 88, claim 44 and page 92, claim 57) and wherein the compound is "a hydrophobic amine" (claims 47, 49, 60 and 62). The specification sets forth methods for screening compounds to identify those that purportedly effect "an alteration in late endosomal/lysosomal trafficking" as well as methods of decreasing melanin production and skin pigmentation using such

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compounds. Nowhere, however, does the specification specify which particular compounds have the desired characteristic of effecting an alteration in late endosomal/lysosomal trafficking, other than those specific compounds set forth in the specification (for example, those compounds disclosed on p. 11, lines 16-29), which are apparently able to generally affect late endosomal/lysosomal trafficking in some unidentified way.

The recitation of an effect desired in a compound in the specification or a claim, even an original claim, does not necessarily satisfy the written description requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Univ. of Rochester v. G.D. Searle*, 69 USPQ2d 1886, 1882 (CAFC 2004). A description of what a material does, rather than what it is, usually does not suffice to provide an adequate written description, it can only do so in accordance with PTO guidelines stating that the requirement can be met by disclosing "sufficiently detailed, relevant identifying characteristics," including "functional characteristics when coupled with a known or disclosed correlation between function and structure." *Univ. of Rochester v. G.D. Searle*, 68 USPQ2d 1424, 1432 (DC WNY 2003). No such correlation has been disclosed in the instant specification; at best, all that can be inferred from the instant specification is that the compounds¹ specifically disclosed (for example, on page 11, lines 16-29) are capable of affecting late endosomal/lysosomal trafficking and are thus useful in the present invention.

Claims 57-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).²

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

¹ Examiner notes that the compounds disclosed in the specification as being effectors of late endosomal/lysosomal trafficking are both functionally and structurally diverse, ranging from progesterone (a hormone), to hydrophobic amines (such as tricyclic antidepressants) and steroid derivatives.

² As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

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- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a method of reducing skin pigmentation comprising contacting the skin with an effective amount of a compound that effects an alteration in late endosomal/lysosomal trafficking. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites

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Virador *et al.* (art on the record) and Seiberg *et al.* (J. Invest. Dermatol., 2000, v. 115, pp. 162-167).

These articles plainly demonstrate that the art of modulating melanogenesis (*i.e.* affecting skin pigmentation with chemical or biological compounds) is very unpredictable. As discussed on page 207, second column of Virador *et al.*, there has been great variation in studies on various bioactive compounds targeted at regulating melanin production. There are many potential approaches for testing the melanogenic effects of bioactive molecules. Screening for bioactive melanogenic compounds requires four discrete steps, quantitating (1) effects on enzymatic activity *in vitro*, (2) effects on cultured normal melanocytes, (3) effects on melanocyte:keratinocyte cocultures, and (4) toxicity and efficacy testing *in vivo*. Virador *et al.*, pp. 209-210, bridging paragraph. Although a compound may be active in various *in vitro* assays, it is not predictable that its application to skin will result in reduced skin pigmentation. This is further exemplified in Seiberg *et al.*, wherein they state that pigmentary disorders can be inherited (*e.g.* vitiligo, Waardenburg syndrome), acquired (*e.g.* postinflammatory pituriasis alba, idiopathic guttate hypomelanosis, melasma), medication related (*e.g.* minocycline, bleomycin, busulfan, zidovudine), and transmitted through infection (*e.g.* tinea versicolor). Hyperpigmentation disorders are often treated with hydroquinones, retinoids, and tyrosinase inhibitors, but results of such treatments are sometimes disappointing. Seiberg *et al.* at p. 162, left column, second paragraph (emphasis added).

Clearly then, the treatment of hyperpigmentary skin conditions, particularly in humans, is extremely unpredictable, especially considering that there are many different causes of skin pigmentation disorders with different etiologies and potential treatments.

2. The breadth of the claims

The claims vary in breadth, some (such as claim 57) vary broadly, reciting a method of "reducing skin pigmentation" with a "compound that effects an alteration in late endosomal/lysosomal trafficking". Others, such as claim 61, are narrower, reciting a specific compound for use in the method. All, however, are extremely broad insofar as they disclose a general method of reducing skin pigmentation (a *per se ex vivo* method) without limitation to a particular skin condition.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to reduce skin pigmentation, particularly in humans. The working examples are limited to *in vitro* assays of melanin production with no guidance on how skilled artisan would (a) formulate a composition for application to the skin and (b) determine whether or not a particular compound reduces skin pigmentation. In addition, there is no reasonable expectation that a compound that effects an alteration in late endosomal/lysosomal trafficking *in vitro* will reduce skin pigmentation *ex vivo* and applicants have offered no

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direction or guidance on how one would test compounds for this desired effect. Thus, the applicant at best has provided specific direction or guidance only for screening compounds that decrease melanin production in a melanocyte. No reasonably specific guidance is provided concerning useful therapeutic protocols for reducing skin pigmentation, especially in humans.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods and compounds could be predictably used to reduce skin pigmentation as inferred in the claims and contemplated by the specification. To practice the claimed invention, the skilled artisan would, in the very least, have to carry out experiments to: 1) determine whether a compound that effects an alteration in late endosomal/lysosomal trafficking *in vitro* is also effective *ex vivo*; 2) formulate a topical composition of said compound; 3) determine whether the compound, when applied to the skin, is absorbed into the skin; and 4) quantitatively assess the compound's effect on skin pigmentation. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation “results in a decrease in melanin product” in Line 4. It is not clear what the product of melanin is because the claim is drawn to a method of decreasing melanin production. In the instant claim, melanin itself is recited in Line 1 as the product being decreased. All claims dependent from Claim 44 carry forth this limitation and are therefore also indefinite.

Conclusion

No claims are allowed. Claims 48 and 50-56 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Examiner
Art Unit 1614

June 19, 2006



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SUPERVISORY PATENT EXAMINER